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| Bell, Boyd & Lloyd LLP 3580 Carmel Mountain Road Suite 200 San Diego, CA 92130 | | | EXAMINER | |
| | | | EPFS FORD, JANET L | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/601,997

Applicant(s)

KECK, JAMES G.

Examiner

Janet L. Epps-Ford

Art Unit

1633

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 May 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-14 and 58-73 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-14 and 58-73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/C2)
- Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 9-14, and 58-73 are presently pending.

Response to Arguments

Claim Rejections - 35 USC § 112

3. Claims 9-14, and 58-73 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record, and for those reasons set forth below.
4. Applicant's arguments filed 5-28-08 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds as amended claims 58 in all instances recites the mRNA transcribed from the target nucleic acid molecule that "comprises the sample nucleic acid sequence in the target nucleic acid molecule." In addition, Applicants state that the claim recites that the oligonucleotide family members all include nucleic acid complementary to the sample, therefore inhibition of expression by the oligonucleotide family is directly associated with the nucleic acid sequence in the target. Therefore, Applicants requested reconsideration of this rejection.
5. Contrary to Applicant's assertions, the instant claims remain ambiguous for the following reasons. Instant claim 58 was amended to recite the following:

58. (Currently Amended) A high-throughput method of assigning a function associated with a product encoded by a sample nucleic acid sequence in a target nucleic acid molecule, said method comprising:

a) without any intervening bacterial cloning steps and without any conformational modeling of ***mRNA transcribed from the sample nucleic*** acid sequence in the target nucleic acid molecule, delivering into and amplifying and expressing a plurality of members of an oligonucleotide family as individual transcription products in a plurality of recombinant non-bacterial host cells comprising the target nucleic acid molecule that comprises the sample nucleic acid sequence, whereby the method is high-throughput, wherein: the oligonucleotide family comprises a plurality of nucleic acid molecules; each member of the oligonucleotide family encodes a transcription product comprising a sequence that is complementary to a sequence contained in ***the mRNA transcribed*** from the target sample nucleic acid sequence in the target nucleic acid molecule;

the plurality of members of the oligonucleotide family are introduced into expression vectors, which are introduced into the host cells, wherein the expression vectors comprise:

double-stranded DNA, comprising: a sense strand and an antisense strand, wherein the sense strand encodes a transcription product that is complementary to and binds to ***an mRNA sequence transcribed*** from the sample nucleic acid sequence in the target nucleic molecule so that expression of a product coded for by the sample nucleic acid sequence is inhibited; and means for determining directionality of expression, wherein the product coded for by the sample nucleic acid sequence is

associated with at least one phenotypic property of a host cell containing the mRNA sequence; and wherein the expression vector is for expression in non-bacterial host cells; the coding sequence for each individual transcription product encodes an antisense nucleic acid that binds to ***the mRNA transcribed*** from the sample nucleic acid sequence in the target nucleic acid molecule; and

expression of one or more of the individual transcription products inhibits production of a product of ***the mRNA***; and

b) in the resulting host cells, comparing the phenotypes of the resulting host cells to phenotypes of control cells to identify changes in phenotype to thereby assign a function associated with the product encoded by the sample nucleic acid sequence in the target nucleic acid molecule, wherein control cells are untransfected host cells, whereby changes in phenotype can be assigned by comparison of the transfected host cell, and the un- transfected host cell.

6. To the extent that there is disagreement between "*the mRNA transcribed*" in line 12, and "*an mRNA sequence transcribed*" in line 19, the above method is ambiguous, since it is unclear if the mRNA referred to line 12 is the same as the "*mRNA transcribed*" in line 19 of this claim.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 8-14, and 58-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. and Draper et al. (US 5,496,698) in view of Gudkov et al. (see PTO-892 of 02-03-2005).

9. Applicant's arguments filed 5-28-08 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that Applicant's amendment to the claims to recite that "the oligonucleotide family inhibits expression of the sample nucleic acid should obviate the rejection." However, contrary to Applicant's assertions, the Examiner's original interpretation of claim 58 as reading on wherein "gene function is assigned based upon the observation of "changes in phenotype" of non-bacterial cells expressing one or more members of an oligonucleotide family that inhibits the expression of an mRNA transcribed from a target nucleic acid sequence.." is equivalent interpretation of what it appears that Applicants are seeking to claim as recited in the presently amended claims.

10. However, Applicants further argued that there are differences between the claimed invention and the prior art. First Applicants argued that Wagner et al. was limited to the use of conformational modeling of mRNA, and thus did not read on the claimed invention. Contrary to Applicant's assertions, although conformational modeling of mRNA is mentioned as a tool for identifying accessible cleavage sites in mRNA, there is a variety of other tools that are disclosed in this reference as useful in this process, which includes merely observing the sequence structure of the mRNA for identifying GUC or CUC sequences in the mRNA. Thus, alternative methods are

provided in Wagner et al. for identifying potential cleavage sites in a target mRNA for ribozyme cleavage (see col. 18, lines 25-39).

11. Moreover, Applicants argued that Wagner et al. teaches the design of discrete ribozyme molecules, however the instant claims comprise the use of a plurality of oligonucleotides having a sequence complementary to the target mRNA. Contrary to Applicant's assertions the instant claims are also drawn to ribozymes, which are not completely complementary to its target, and therefore require a "design" step. According to the specification as filed, ribozymes are designed based upon the identification of the GUC triplet in the target mRNA, see page 7, 2nd paragraph of the specification as filed, which is one of the means described by Wagner et al.

12. Applicants further argued that Wagner et al. fails to teach or suggest a high-throughput method of assigning a function. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

13. In regards to Draper et al., Applicants argued that Draper et al. does not provide for a method for assigning a function to a gene product by inhibiting the expression of the gene product using a family of oligonucleotides whose sequences are based on a sample in the target. Again, Applicants are attempting to show nonobviousness by attacking Draper et al. individually. Contrary to Applicant's assertions, the Draper et al. reference is provided to set forth what was known in the prior art regarding the design

and use of a combinatorial library of ribozyme molecules, particularly wherein a population of ribozymes having different substrate binding arms, and targeting the same mRNA, is introduced into a population of cells including a target RNA molecule. The cells are designed such that only those cells including a useful ribozyme will provide a detectable signal. Moreover, contrary to Applicant's assertions, due to the teachings of Draper et al. which define a large scale screen of a plurality of ribozymes in a population of cells, absent evidence to the contrary, the teachings of Draper et al. are amenable to a high throughput process for assigning an activity to a target mRNA in a cell, namely inhibition.

14. In response to Gudkov et al., Applicants argue that Gudkov et al. is directed to the use of a random expression library, which does not comprise the assigning of a function to a product encoded by known sequence of interest. Contrary to Applicant's assertions, the genetic suppressor elements of GSE's of Gudkov et al. are not random fragments, having no relationship to a target nucleic acid. Gudkov et al. clearly teach that the GSE's are described as follows:

"[I]n a first aspect, the invention provides a method for identifying GSEs that confer upon untransformed cells the transformed phenotype of malignant mammalian cells. The GSEs identified by this method will be homologous to a gene that is associated with the transformed phenotype of malignant mammalian cells. For purposes of the invention, the term "homologous to a gene" has two different meanings, depending on whether the GSE acts through an antisense or antigene mechanism, or through a mechanism of interference at the protein level. In the former case, a GSE that is an antisense or antigene oligonucleotide or polynucleotide is homologous to a gene if it has a nucleotide sequence that hybridizes under physiological conditions to the gene or its mRNA transcript by Hoogsteen or Watson-Crick base-pairing."

The GSE's of Gudkov et al. clearly encompass both antigene and antisense sequences which hybridize to a target mRNA transcript or to a gene, wherein GSE's are to be delivered to eukaryotic cells to test or determine the ability of these nucleic acid

fragments to function as genetic suppressor elements (GSE) (see col. 10-12). The methods of Gudkov et al. essentially comprise methods for identifying gene function since the ability of the putative nucleic acid molecules to function, as a GSE is unknown prior to testing. Moreover, the methods of Gudkov et al. do not recite intervening bacterial cloning steps or conformational modeling as recited in the instant claims.

Contrary to Applicant's assertions, and absent any evidence to the contrary, as stated in the prior Office Action, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the teachings of Wagner et al. and Draper et al. with the teachings of Gudkov et al. in the design of the instant invention. One of ordinary skill in the art would have been motivated to make this modification since Wagner et al. and Draper et al. expressly state that their disclosed methods for determining gene function encompass wherein the transfection method comprises the use of retroviral vectors, and the teachings of Gudkov et al. are specifically designed to deliver nucleic acid to cells using retroviral vectors with the express purpose of determining their ability to alter a phenotype of the transfected cells.

In regards to Applicant's arguments that none of the cited references teaches or suggests a high throughput method of assigning a gene function nor elimination of any intervening bacterial cloning steps, since it is clear that the prior art teaches method for using antiense/ribozymes to inhibit gene function, and thus observe phenotype associated with this inhibition, it would have been obvious to the ordinary skilled artisan to design a system that would provide this method in a faster more efficient process, i.e. in a "high throughput" method. Moreover, in regards to the non-bacterial cloning step,

this limitation merely eliminates a processing step, which one of ordinary skill in the art would have increased the productivity of the method, see MPEP § 2143 which recites: “[T]he Courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Id.* at 1366, 80 USPQ2d at 1649. “[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement’ is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references.” *Id.* at 1368, 80 USPQ2d at 1651.”

Applicant's arguments do not take the place of evidence of nonobviousness, absent evidence to the contrary, the claims remain rejected for the reasons of record.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE